~~10439263~~ 10/561,944

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	OCT 23	The Derwent World Patents Index suite of databases on STN has been enhanced and reloaded
NEWS 4	OCT 30	CHEMLIST enhanced with new search and display field
NEWS 5	NOV 03	JAPIO enhanced with IPC 8 features and functionality
NEWS 6	NOV 10	CA/CAplus F-Term thesaurus enhanced
NEWS 7	NOV 10	STN Express with Discover! free maintenance release Version 8.01c now available
NEWS 8	NOV 20	CA/CAplus to MARPAT accession number crossover limit increased to 50,000
NEWS 9	DEC 01	CAS REGISTRY updated with new ambiguity codes
NEWS 10	DEC 11	CAS REGISTRY chemical nomenclature enhanced
NEWS 11	DEC 14	WPIDS/WPINDEX/WPIX manual codes updated
NEWS 12	DEC 14	GBFULL and FRFULL enhanced with IPC 8 features and functionality
NEWS 13	DEC 18	CA/CAplus pre-1967 chemical substance index entries enhanced with preparation role
NEWS 14	DEC 18	CA/CAplus patent kind codes updated
NEWS 15	DEC 18	MARPAT to CA/CAplus accession number crossover limit increased to 50,000
NEWS 16	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS 17	DEC 27	CA/CAplus enhanced with more pre-1907 records
NEWS 18	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 19	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 20	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS 21	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 22	JAN 22	CA/CAplus updated with revised CAS roles
NEWS 23	JAN 22	CA/CAplus enhanced with patent applications from India
NEWS 24	JAN 29	PHAR reloaded with new search and display fields
NEWS 25	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS 26	FEB 13	CASREACT coverage to be extended
NEWS 27	Feb 15	PATDPASPC enhanced with Drug Approval numbers
NEWS 28	Feb 15	RUSSIAPAT enhanced with pre-1994 records

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

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FILE 'HOME' ENTERED AT 11:27:51 ON 19 FEB 2007

=> FILE REG

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 11:28:00 ON 19 FEB 2007
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DICTIONARY FILE UPDATES: 18 FEB 2007 HIGHEST RN 921759-52-6

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TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

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http://www.cas.org/ONLINE/UG/regprops.html

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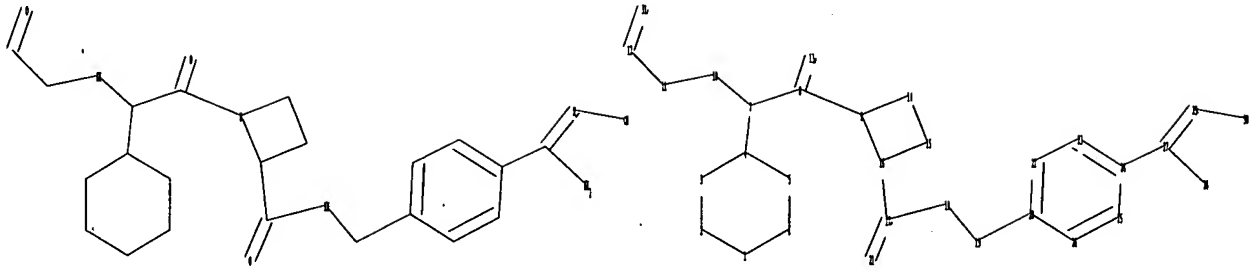
Uploading C:\Program Files\Stnexp\Queries\10439263.str



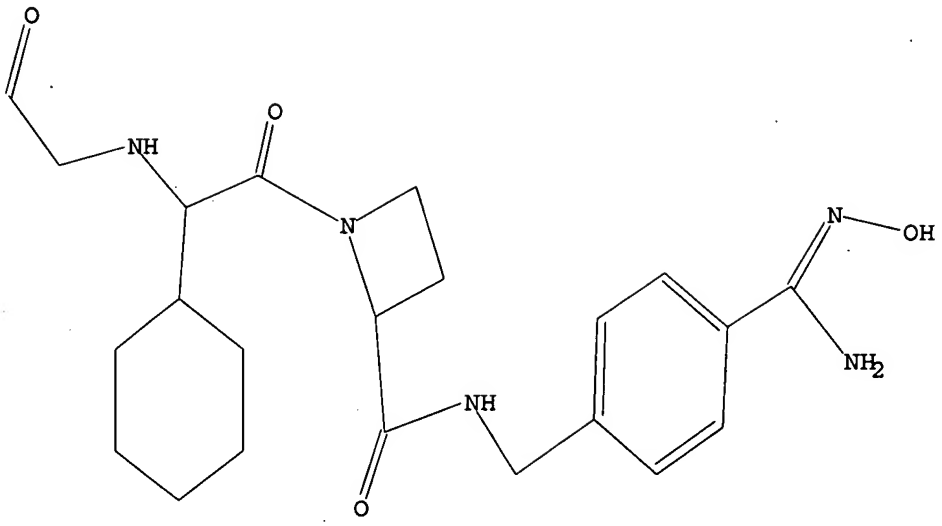
chain nodes :
7 8 10 11 12 13 17 18 19 21 27 28 29 30 31
ring nodes :
1 2 3 4 5 6 9 14 15 16 20 22 23 24 25 26
chain bonds :
4-7 7-8 7-10 8-9 8-13 10-11 11-12 12-31 16-17 17-18 17-21 18-19 19-20
24-27 27-28 27-29 29-30
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-14 9-16 14-15 15-16 20-22 20-26 22-23 23-24
24-25 25-26
exact/norm bonds :
7-10 8-9 8-13 9-14 9-16 10-11 12-31 14-15 15-16 17-18 17-21 18-19 27-28
27-29 29-30
exact bonds :
1-2 1-6 2-3 3-4 4-5 4-7 5-6 7-8 11-12 16-17 19-20 24-27
normalized bonds :
20-22 20-26 22-23 23-24 24-25 25-26
isolated ring systems :
containing 1 : 9 : 20 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:Atom 10:CLASS
11:CLASS 12:CLASS 13:CLASS 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS
19:CLASS 20:Atom 21:CLASS 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:CLASS
28:CLASS 29:CLASS 30:CLASS 31:CLASS

L1 STRUCTURE UPLOADED

=> D
L1 HAS NO ANSWERS
L1 STR

SAEED



Structure attributes must be viewed using STN Express query preparation.

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=> S L1
SAMPLE SEARCH INITIATED 11:28:21 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       32 TO ITERATE

100.0% PROCESSED       32 ITERATIONS                          2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          301 TO      979
PROJECTED ANSWERS:               2 TO      124

L2            2 SEA SSS SAM L1

=>
Uploading C:\Program Files\Stnexp\Queries\104392631.str
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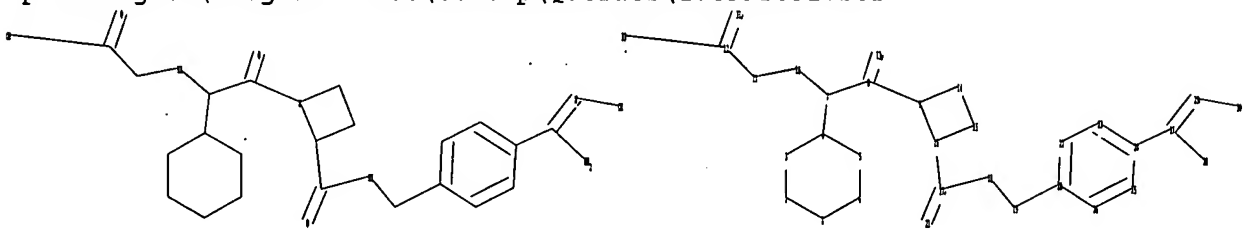

chain nodes :

SAEED

```
7  8  10  11  12  13  17  18  19  21  27  28  29  30  31  33
ring nodes :
1  2  3  4  5  6  9  14  15  16  20  22  23  24  25  26
chain bonds :
4-7  7-8  7-10  8-9  8-13  10-11  11-12  12-31  12-33  16-17  17-18  17-21  18-19
19-20  24-27  27-28  27-29  29-30
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  9-14  9-16  14-15  15-16  20-22  20-26  22-23  23-24
24-25  25-26
exact/norm bonds :
7-10  8-9  8-13  9-14  9-16  10-11  14-15  15-16  17-18  17-21  18-19  27-28  27-29
 29-30
exact bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  7-8  11-12  16-17  19-20  24-27
normalized bonds :
12-31  12-33  20-22  20-26  22-23  23-24  24-25  25-26
isolated ring systems :
containing 1 : 9 : 20 :

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:CLASS  8:CLASS  9:Atom  10:CLASS
11:CLASS  12:CLASS  13:CLASS  14:Atom  15:Atom  16:Atom  17:CLASS  18:CLASS
19:CLASS  20:Atom  21:CLASS  22:Atom  23:Atom  24:Atom  25:Atom  26:Atom  27:CLASS
28:CLASS  29:CLASS  30:CLASS  31:CLASS  33:CLASS



L3      STRUCTURE UPLOADED

=> D
L3 HAS NO ANSWERS
L3              STR

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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=> S L3
SAMPLE SEARCH INITIATED 11:30:29 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       32 TO ITERATE

100.0% PROCESSED       32 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          301 TO      979
PROJECTED ANSWERS:               0 TO        0

L4            0 SEA SSS SAM L3

=> S L3 FULL
FULL SEARCH INITIATED 11:30:36 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      644 TO ITERATE

100.0% PROCESSED      644 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01


SAEED
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L5 1 SEA SSS FUL L3

=> FILE CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	173.45	173.66

FILE 'CAPLUS' ENTERED AT 11:30:41 ON 19 FEB 2007
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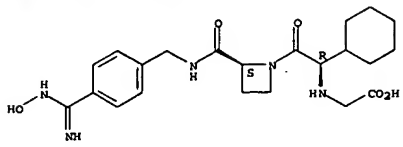
=> S L5
L6 13 L5

=> D IBIB ABS HITSTR TOT

L6 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:460730 CAPLUS
DOCUMENT NUMBER: 145:201989
TITLE: Influence of erythromycin on the pharmacokinetics of ximelagatran may involve inhibition of P-glycoprotein-mediated excretion
AUTHOR(S): Eriksson, Ulf G.; Dorani, Hassan; Karlsson, Johan; Fritsch, Holger; Hoffmann, Kurt-Jurgen; Olsson, Lia; Sarich, Troy C.; Wall, Ulrika; Schutzer, Kaja-Marie
CORPORATE SOURCE: AstraZeneca R and D, Moelndal, Swed.
SOURCE: Drug Metabolism and Disposition (2006), 34(5), 775-782
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A pharmacokinetic interaction between erythromycin and ximelagatran, an oral direct thrombin inhibitor, was demonstrated in this study in healthy volunteers. To investigate possible interaction mechanisms, the effects of erythromycin on active transport mediated by P-glycoprotein (P-gp) in vitro in Caco-2 and P-gp-over-expressing Madin-Darby canine kidney-human multidrug resistance-1 cell prepns. and on biliary excretion of melagatran in rats were studied. In healthy volunteers (seven males and nine females; mean age 24 years) receiving a single dose of ximelagatran 36 mg on day 1, erythromycin 500 mg t.i.d. on days 2 to 5, and a single dose of ximelagatran 36 mg plus erythromycin 500 mg on day 6, the least-squares mean ests. (90% confidence intervals) for the ratio of ximelagatran with erythromycin to ximelagatran given alone were 1.82 (1.64-2.01) for the area under the concentration-time curve and 1.74 (1.52-2.00) for the maximum plasma concentration of melagatran, the active form of ximelagatran. Neither the slope nor the intercept of the melagatran plasma concentration-effect relationship for activated partial thromboplastin time statistically significantly differed as a function of whether or not erythromycin was administered with ximelagatran. Ximelagatran was well tolerated regardless of whether it was administered with erythromycin. Erythromycin inhibited P-gp-mediated transport of both ximelagatran and melagatran in vitro and decreased the biliary excretion of melagatran in the rat. These results indicate that the mechanism of the pharmacokinetic interaction between oral ximelagatran and erythromycin may involve inhibition of transport proteins, possibly P-gp, resulting in decreased melagatran biliary excretion and increased bioavailability of melagatran.
IT 192939-72-3
RL: BSU (Biological study, unclassified); FMU (Formation, unclassified); BIOL (Biological study); FORM (Formation, nonpreparative)
(erythromycin effect on ximelagatran pharmacokinetics: P-gp mediation)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

L6 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

Absolute stereochemistry.

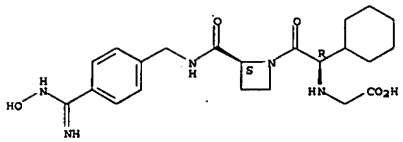


REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:498725 CAPLUS
DOCUMENT NUMBER: 143:126331
TITLE: The oral direct thrombin inhibitor, ximelagatran, an alternative for anticoagulant treatment during the puerperium and lactation
AUTHOR(S): Hellgren, M.; Johansson, S.; Eriksson, U. G.; Wahlander, K.
CORPORATE SOURCE: Department of Antenatal Care, Primary Health Care South Bohuslaen and Institute for the Health of Women and Children, University of Goeteborg, Swed.
SOURCE: BJOG (2005), 112(5), 579-583
CODEN: BIOGFO; ISSN: 1470-0328
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To determine the excretion of the oral direct thrombin inhibitor (oral DTI), ximelagatran, and its active form, melagatran, in human milk, and to thus evaluate the potential exposure of breastfed infants to melagatran. Design: An open, single dose, single center study. Setting: Department of Antenatal Care, Primary Health Care South Bohuslaen and Institute for the Health of Woman and Children, Goeteborg University, Sweden. Sample: Seven healthy Caucasian breastfeeding women who were at least two months postpartum were studied. Methods: The concns. of ximelagatran, its two intermediates, and melagatran were determined using liquid chromatog.-mass spectrometry, with the limit of quantification of 2 nmol L-1 for human milk and 10 nmol L-1 for plasma concns. Main outcome measures: Concns. of ximelagatran, its intermediates and melagatran were measured in breast milk over 72 h, and in plasma over 12 h, after a single oral 36 mg dose of ximelagatran. Results: Neither ximelagatran nor its intermediates were detected in human breast milk. Only trace amts. of melagatran were detected. The mean cumulative amount of melagatran excreted into breast milk over the 72-h period after dosing with oral ximelagatran was 0.00091% of the administered dose of ximelagatran. Ximelagatran was well tolerated, with no clin. relevant changes in laboratory variables or vitals signs. Conclusions: Trace levels of melagatran are excreted in human breast milk following administration of the oral DTI ximelagatran. The exposure of breastfed infants to melagatran appears to be low and is therefore unlikely to be of clin. concern.
IT 192939-72-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ximelagatran intermediate, hydroxy-melagatran was not excreted in breast milk of Caucasian woman after oral DTI, ximelagatran administration)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

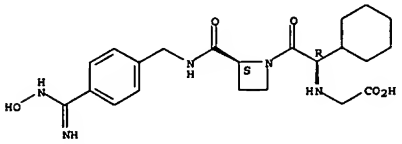


REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:314009 CAPLUS
DOCUMENT NUMBER: 143:381615
TITLE: Characterization and partial purification of the rat and human enzyme systems active in the reduction of N-hydroxymelagatran and benzamidoxime
AUTHOR(S): Andersson, Susanne; Hofmann, Yvonne; Nordling, Asa; Li, Xue-qing; Nivelius, Sabina; Andersson, Tommy B.; Ingelman-Sundberg, Magnus; Johansson, Inger
CORPORATE SOURCE: Division of Molecular Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Swed.
SOURCE: Drug Metabolism and Disposition (2005), 33(4), 570-578
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The enzymic basis for intracellular reduction of N-hydroxylated amidines to their corresponding amidines, and hydroxylamines to their corresponding amines, is unknown. The hydroxylated amidines can be used as prodrug moieties, and an understanding of the enzyme system active in the reduction can contribute to more efficient drug development. In this study, we examined the properties of this enzyme system using benzamidoxime and N-hydroxymelagatran as substrates. In rats and humans, the hepatic enzyme system was localized in mitochondria as well as in microsomes, using preferably NADH as cofactor. Potassium cyanide, N-methylhydroxylamine, p-hydroxymercuribenzoate, and desferrioxamine were efficient inhibitors, whereas typical cytochrome P 450 inhibitors were ineffective. In rats, the highest specific activity was found in liver, adipose tissue, and kidneys, whereas in humans, the specific activity in the prepns. of adipose tissue examined was lower. A sex difference was observed in rat liver, where 4-fold higher activity was seen in microsomes from female rats. No gender differences were present in any other tissue investigated. Partial purification of the hepatic system was achieved using polyethylene glycol fractionation followed by Octyl Sepharose chromatog. at low detergent concns., whereas the enzyme was denatured after complete solubilization. The unique appearance of the enzyme activity in adipose tissue, together with the cyanide sensitivity and the failure of typical P 450 inhibitors to impede the reaction, indicates that the enzyme system active in reduction of benzamidoxime and N-hydroxymelagatran formation is not of cytochrome P 450 origin, but likely consists of an NADH-dependent electron transfer chain with a cyanide-sensitive protein as the terminal component.
IT 192939-72-3, Melagatran hydroxyamidine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(characterization and partial purification of rat and human enzyme systems active in reduction of N-hydroxymelagatran and benzamidoxime)
RN 192939-72-3 CAPLUS

L6 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



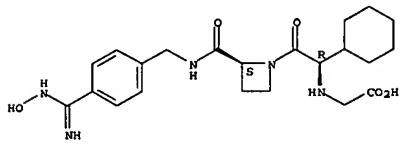
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1156571 CAPLUS
DOCUMENT NUMBER: 142:56674
TITLE: New process for the production of melagatran
INVENTOR(S): Grehn, Marcus; Musil, Tibor; Sjoegren, Magnus
PATENT ASSIGNEE(S): Astrazeneca Ab, Swed.
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113364	A1	20041229	WO 2004-SE1016	20040623
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004249658	A1	20041229	AU 2004-249658	20040623
CA 2528930	A1	20041229	CA 2004-2528930	20040623
EP 1641814	A1	20060405	EP 2004-749054	20040623
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1809585	A	20060726	CN 2004-80017545	20040623
BR 2004011769	A	20060808	BR 2004-11769	20040623
NO 2005005925	A	20060119	NO 2005-5925	20051213
US 2006178312	A1	20060810	US 2005-561944	20051221
PRIORITY APPLN. INFO.:			SE 2003-1879 A	20030625
			WO 2004-SE1016 W	20040623

OTHER SOURCE(S): CASREACT 142:56674; MARPAT 142:56674
AB A process for the production of melagatran [HO2CCH2-(R)Cgl-(S)Aze-Pab-H, where Cgl is cyclohexylglycinyl, Aze is azetidine-2-carbonyl, and Pab is p-amidinobenzylamino] comprises the hydrolysis of an N-hydroxymelagatran alkyl or benzyl ester and reduction of the intermediate N-hydroxymelagatran. Thus, ximelagatran in ethanolic NaOH solution was stirred for four hours at 20-25°C to afford 90 weight % N-hydroxymelagatran, which was hydrogenated over 5% Pd/C to afford melagatran.
IT 192939-72-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(production of melagatran from N-hydroxymelagatran esters)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

L6 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Absolute stereochemistry.



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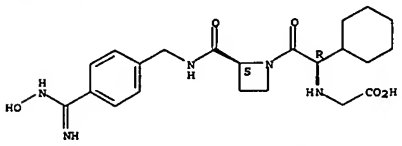
App'l cont's

SAEED

L6 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:304716 CAPLUS
DOCUMENT NUMBER: 142:62413
TITLE: Bioequivalence of ximelagatran, an oral direct thrombin inhibitor, as whole or crushed tablets or dissolved formulation
AUTHOR(S): Schuetzer, Kajs-Marie; Wall, Ulrika; Loennerstedt, Carina; Ohlsson, Lis; Teng, Renli; Sarich, Troy C.; Eriksson, Ulf G.
CORPORATE SOURCE: R+D Moelndal, AstraZeneca, Moelndal, Swed.
SOURCE: Current Medical Research and Opinion (2004), 20(3), 325-331
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: LibraPharm Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To investigate whether crushed or dissolved tablets of the oral direct thrombin inhibitor ximelagatran are bioequivalent to whole tablet administration. Ximelagatran is currently under development for the prevention and treatment of thromboembolic disorders. Research design and methods: This was an open-label, randomized, three-period, three-treatment crossover study in which 40 healthy volunteers (aged 20-33 yr) received a single 36-mg dose of ximelagatran administered in three different ways: I swallowed whole, II crushed, mixed with applesauce and ingested and III dissolved in water and administered via nasogastric tube. Results: The plasma concns. of ximelagatran, its intermediates and the active form melagatran were determined Ximelagatran was rapidly absorbed and the bioavailability of melagatran was similar after the three different administrations, fulfilling the criteria for bioequivalence. The mean area under the plasma concentration-vs.-time curve (AUC) of melagatran was 1.6 μmol·h/L (ratio 1.01 for treatment II/I and 0.97 for treatment III/I), the mean peak concentration (Cmax) was 0.3 μmol/L (ratio 1.04 for treatment II/I and 1.02 for treatment III/I) and the mean half-life (t1/2) was 2.8h for all treatments. The time to Cmax (tmax) was 2.2 h for the whole tablet and approx. 0.5 h earlier when the tablet was crushed or dissolved (1.7-1.8 h), due to a more rapid absorption. The study drug was well tolerated as judged from the low incidence and type of adverse events reported. Conclusion: The present study showed that the pharmacokinetics (AUC and Cmax) of melagatran were not significantly altered whether ximelagatran was given orally as a crushed tablet mixed with applesauce or dissolved in water and given via nasogastric tube.
IT 192939-72-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bioequivalence of ximelagatran as whole or crushed tablets or dissolved formulation)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-

L6 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

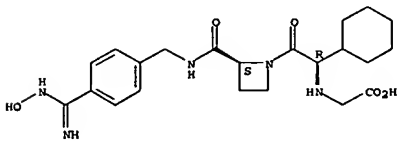


REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:701571 CAPLUS
DOCUMENT NUMBER: 140:138746
TITLE: Ximelagatran, an oral direct thrombin inhibitor, has a low potential for cytochrome P450-mediated drug-drug interactions
AUTHOR(S): Bredberg, Eva; Andersson, Tommy B.; Frison, Lars; Thuresson, Annelie; Johansson, Susanne; Eriksson-Lepkowska, Maria; Larsson, Marita; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca R and D, Moelndal, Swed.
SOURCE: Clinical Pharmacokinetics (2003), 42(8), 765-777
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Ximelagatran is an oral direct thrombin inhibitor currently in clin. development for the prevention and treatment of thromboembolic disorders. After oral administration, ximelagatran is rapidly absorbed and extensively bioconverted, via two intermediates (ethyl-melagatran and hydroxy-melagatran), to its active form, melagatran. In vitro studies have shown no evidence for involvement of cytochrome P 450 (CYP) enzymes in either the bioactivation or the elimination of melagatran. Objective: To investigate the potential of ximelagatran, the intermediates ethyl-melagatran and hydroxy-melagatran, and melagatran to inhibit the CYP system in vitro and in vivo, and the influence of three CYP substrates on the pharmacokinetics of melagatran in vivo. Methods: The CYP inhibitory properties of ximelagatran, the intermediates and melagatran were tested in vitro by two different methods, using heterologously expressed enzymes or human liver microsomes. Diclofenac (CYP2C9), diazepam (CYP2C19) and nifedipine (CYP3A4) were chosen for coadministration with ximelagatran in healthy volunteers. Subjects received oral ximelagatran 24 mg and/or diclofenac 50 mg, a 10-min i.v. infusion of diazepam 0.1 mg/kg, or nifedipine 60 mg. The plasma pharmacokinetics of melagatran, diclofenac, diazepam, N-desmethyl-diazepam and nifedipine were determined when administered alone and in combination with ximelagatran. Results: No inhibition, or only minor inhibition, of CYP enzymes by ximelagatran, the intermediates or melagatran was shown in the in vitro studies, suggesting that ximelagatran would not cause CYP-mediated drug-drug interactions in vivo. This result was confirmed in the clin. studies. There were no statistically significant differences in the pharmacokinetics of diclofenac, diazepam and nifedipine on coadministration with ximelagatran. Moreover, there were no statistically significant differences in the pharmacokinetics of melagatran when ximelagatran was administered alone or in combination with diclofenac, diazepam or nifedipine. Conclusion: As ximelagatran did not exert a significant effect on the hepatic CYP isoenzymes responsible for the metabolism of diclofenac, diazepam and nifedipine, it is reasonable to expect that it would have no effect on the metabolism of other drugs metabolized by these isoenzymes. Furthermore, the pharmacokinetics of melagatran after oral administration of ximelagatran are not expected to be altered by inhibition or induction of CYP2C9, CYP2C19 or CYP3A4. Together, the in vitro and in vivo studies indicate

L6 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
that metabolic drug-drug interactions involving the major human CYP enzymes should not be expected with ximelagatran.
IT 192939-72-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); BIOL (Biological study)
(oral direct thrombin inhibitor ximelagatran has low potential for cytochrome P 450-mediated drug-drug interactions in vitro and in vivo in humans)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

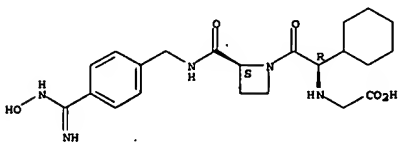
L6 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:701570 CAPLUS
DOCUMENT NUMBER: 139:270230
TITLE: No influence of mild-to-moderate hepatic impairment on the pharmacokinetics and pharmacodynamics of ximelagatran, an oral direct thrombin inhibitor
AUTHOR(S): Wahlander, Karin; Eriksson-Lepkowska, Maria; Frison, Lars; Pager, Gunnar; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca R and D, Moelndal, Swed.
SOURCE: Clinical Pharmacokinetics (2003), 42(8), 755-764
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The oral direct thrombin inhibitor ximelagatran is a new class of anticoagulant currently in clin. development for the prevention and treatment of thromboembolic disease. After oral administration, ximelagatran is rapidly absorbed and bioconverted to its active form melagatran. Objective: To investigate the influence of mild-to-moderate hepatic impairment on the pharmacokinetic and pharmacodynamic properties of ximelagatran. Study design: Nonblinded, nonrandomised study. Participants: Twelve volunteers with mild-to-moderate hepatic impairment (classified as Child-Pugh A or B) and 12 age-, weight-, and sex-matched control volunteers with normal hepatic function. Methods: Volunteers received a single oral dose of ximelagatran 24mg. Plasma and urine samples were collected for pharmacokinetic and pharmacodynamic analyses. Results: The absorption and bioconversion of ximelagatran to melagatran were rapid in both groups. The maximum plasma concentration of melagatran (Cmax) was achieved 2-3 h after administration; the mean elimination half-life (t1/2z) was 3.6 h for hepatically impaired volunteers and 3.1 h for the control volunteers. The area under the plasma concentration-time curve (AUC) and Cmax of melagatran in volunteers with hepatic impairment were 11 and 25% lower than in control volunteers, resp. However, after correcting for the higher renal function (i.e. higher calculated creatinine clearance) in the hepatically impaired volunteers, the ratio of melagatran AUC for hepatically impaired/control volunteers was 0.98 (90% CI 0.80, 1.22), suggesting that mild-to-moderate hepatic impairment had no influence on the pharmacokinetics of ximelagatran. Melagatran was the predominant compound in urine, accounting for 13-14% of the ximelagatran dose. Renal clearance of melagatran was 13% higher in hepatically impaired than in control volunteers. There were no significant differences between the two groups in the concentration-response relation between plasma melagatran concentration and activated partial thromboplastin time (APTT). Baseline prothrombin time (PT) was slightly longer in the hepatically impaired patients than in the control volunteers, probably reflecting a slight decrease in the activity of coagulation factors. However, when concns. of melagatran were at their peak, the increase in PT from baseline values was the same in both groups. Capillary bleeding time was measured in the hepatically impaired patients only, and was not increased by ximelagatran. Ximelagatran was well tolerated in both groups. Conclusion: There were no differences in the pharmacokinetic or pharmacodynamic properties of melagatran following oral administration of ximelagatran between the hepatically impaired and control volunteers. These findings suggest that dose adjustment for patients with mild-to-moderate impairment of hepatic function is not necessary.

IT 192939-72-3, Melagatran hydroxyamidine
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(no influence of mild-to-moderate hepatic impairment on pharmacokinetics and pharmacodynamics of ximelagatran (Exanta))

RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

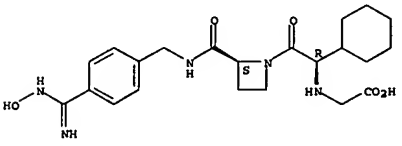
L6 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:497014 CAPLUS
DOCUMENT NUMBER: 139:390673
TITLE: No influence of obesity on the pharmacokinetics and pharmacodynamics of melagatran, the active form of the oral direct thrombin inhibitor ximelagatran
AUTHOR(S): Sarich, Troy C.; Teng, Renli; Peters, Gary R.; Wollbratt, Maria; Homolka, Robert; Svensson, Mia; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca LP, Wilmington, DE, USA
SOURCE: Clinical Pharmacokinetics (2003), 42(5), 485-492
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Ximelagatran, an oral direct thrombin inhibitor, is currently in clin. development for the prevention and treatment of thromboembolic disease. Following oral administration, ximelagatran undergoes rapid bioconversion to its active form, melagatran, via two minor intermediates. Obesity, defined as body mass index (BMI) >30 kg/m2, is a recognized risk factor for thrombosis. There is potential for differences in the pharmacokinetics and pharmacodynamics of drugs administered to obese vs. non-obese patients, and some drugs may require alternative administration strategies in obese patients. Objective: To investigate the effect of obesity on the pharmacokinetics and pharmacodynamics of melagatran after oral administration of ximelagatran. Design and participants: This was an open-label, single-dose, group-matched study in which obese subjects (BMI 32-39 kg/m2; six male and six female; age 21-40 yr) were matched by sex and age (±2 yr) with non-obese subjects (BMI 21-26 kg/m2; six male and six female; aged 21-39 yr). Each subject received a single oral dose of ximelagatran 24mg. Blood samples for determination of plasma concns. of melagatran and activated partial thromboplastin times (APTT; a marker of melagatran pharmacodynamics) were collected up to 12 h after administration. Results: There were no statistically significant differences in the pharmacokinetic properties of melagatran between obese and non-obese subjects. Values of area under the melagatran plasma concentration-time curve, maximum plasma concentration, (Cmax), time at which Cmax occurred and terminal elimination half-life were approx. 1 μmol • h/L, 0.2 μmol/L, 2 h and 3 h in both obese and non-obese subjects, resp. In addition, there was no statistically significant difference between the obese and non-obese subjects in the amount of ximelagatran, melagatran or the minor intermediates ethyl-melagatran and melagatran hydroxyamidine excreted in urine. When relating the prolongation of APTT ratio to the square root of plasma concentration of melagatran and obesity status (no/yes), no statistically significant interaction between plasma concentration and obesity status was observed. Ximelagatran was well tolerated in both obese and non-obese subjects, and no bleeding events or serious adverse events occurred. Conclusion: No differences in the pharmacokinetics or pharmacodynamics of melagatran were detected between obese and non-obese subjects after oral administration of ximelagatran, suggesting that dose adjustment of ximelagatran in obesity (BMI up to 39 kg/m2) is not necessary.

IT 192939-72-3, Melagatran hydroxyamidine
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(influence of obesity on the pharmacokinetics and pharmacodynamics of melagatran)

RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

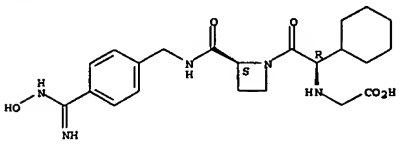
Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:497013 CAPLUS
DOCUMENT NUMBER: 139:390672
TITLE: No influence of ethnic origin on the pharmacokinetics and pharmacodynamics of melagatran following oral administration of ximelagatran, a novel oral direct thrombin inhibitor, to healthy male volunteers
AUTHOR(S): Johansson, Linda C.; Andersson, Magnus; Fager, Gunnar; Gustafsson, David; Eriksson, Ulf G.
CORPORATE SOURCE: AstraZeneca R&D, Moelndal, Swed.
SOURCE: Clinical Pharmacokinetics (2003), 42(5), 475-484
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To determine the influence of ethnic origin on the pharmacokinetic and pharmacodynamic properties of melagatran after oral administration of ximelagatran, a novel oral direct thrombin inhibitor. Study design: This was an open-label, non-randomized study with a single study session. Subjects: Thirty-six young healthy male subjects living in France were divided equally according to their ethnic origin (African, Asian and Caucasian). Methods: All subjects received a single 50mg oral dose of ximelagatran in solution Blood and urine samples for pharmacokinetic evaluation were collected up to 12 and 24 h after administration, resp. Blood samples were also collected to determine the activated partial thromboplastin time (APTT), an ex vivo coagulation time measurement used to demonstrate inhibition of thrombin, up to 24 h after administration. Results: The absorption of ximelagatran, and its bioconversion to melagatran, was rapid in all three ethnic groups. The metabolite pattern in plasma and urine was similar in all groups, with melagatran being the dominant compound For ximelagatran, the mean area under the plasma concentration-time curve (AUC) was similar in the three groups, suggesting that there was no difference in the extent to which ximelagatran was absorbed. Melagatran AUC was higher in the Asian subjects, with a mean Asian/Caucasian ratio (95% CI) of 1.23 (1.04, 1.45). This was presumably because of their lower bodyweight, which is correlated to lower renal function. Following normalization for bodyweight, there were no statistically significant differences between the three ethnic groups. This finding suggests that renal elimination was lower for Asian subjects, whereas there were no differences in the conversion of ximelagatran to melagatran. The interindividual variability of melagatran AUC was low (coefficient of variation 19-26%), and the mean bioavailability of melagatran, estimated using a mean value for melagatran clearance obtained from Caucasian subjects in a previous study, was approx. 20% in all groups (range of mean values 19-23%). APTT increased nonlinearly with increasing melagatran plasma concentration, and no difference in the concentration-response relationship was observed between the groups. Conclusion: After oral administration of ximelagatran, the pharmacokinetic and pharmacodynamic properties of melagatran are independent of ethnic origin. The elimination of melagatran is correlated with renal function.
IT 192939-72-3, Melagatran hydroxyamidine
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(influence of ethnic origin on the pharmacokinetics and pharmacodynamics of melagatran following oral administration of ximelagatran to healthy male volunteers)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

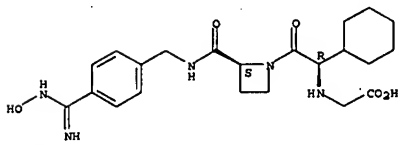
Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:325363 CAPLUS
DOCUMENT NUMBER: 139:270214
TITLE: Characterization of in vitro biotransformation of new, orally active, direct thrombin inhibitor ximelagatran, an amidoxime and ester prodrug
AUTHOR(S): Clement, Bernd; Lopian, Katrin
CORPORATE SOURCE: Pharmaceutical Institute, Christian-Albrechts-University of Kiel, Kiel, Germany
SOURCE: Drug Metabolism and Disposition (2003), 31(5), 645-651
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-Hydroxylated amidines (amidoximes) can be used as prodrugs of amidines. The prodrug principle was developed in our laboratory for pentamidine and had been applied to several other drug candidates. One of these compds. is melagatran, a novel, synthetic, low mol. weight, direct thrombin inhibitor. To increase the poor oral bioavailability due to its strong basic amidine functionality selected to fit the arginine side pocket of thrombin, the less basic N-hydroxylated amidine was used in addition to an Et ester-protecting residue. The objective of this investigation was to study the reduction and the hydrolytic metabolism of ximelagatran via two mono-prodrugs (N-hydroxy-melagatran and ethyl-melagatran) to melagatran by in vitro expts. New high-performance liquid chromatog. methods were developed to analyze all four compds. The biotransformation of ximelagatran to melagatran involving the reduction of the amidoxime function and the ester cleavage could be demonstrated in vitro by microsomes and mitochondria from liver and kidney of pig and human, and the kinetic parameters were determined So far, one enzyme system capable of reducing N-hydroxylated structures has been identified in pig liver microsomes, consisting of cytochrome b5, NADH-cytochrome b5 reductase, and a P 450 isoenzyme of the subfamily 2D. This enzyme system also reduces ximelagatran and N-hydroxy-melagatran. The participation of recombinant human CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4 with cytochrome b5 and b5 reductase in the reduction can be excluded. In summary, ximelagatran and N-hydroxy-melagatran are easily reduced by several enzyme systems located in microsomes and mitochondria of different organs.
IT 192939-72-3, N-Hydroxymelagatran
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(in vitro biotransformation of ximelagatran, an amidoxime and ester prodrug, and role of microsomal and mitochondrial enzymes)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

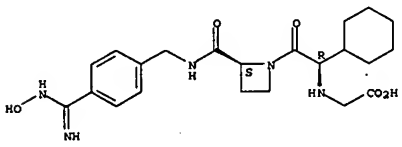
L6 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:156659 CAPLUS
DOCUMENT NUMBER: 139:223644
TITLE: Absorption, distribution, metabolism, and excretion of ximelagatran, an oral direct thrombin inhibitor, in rats, dogs, and humans
AUTHOR(S): Eriksson, Ulf G.; Bredberg, Ulf; Hoffmann, Kurt-Jurgen; Thuresson, Anneli; Gabrielsson, Margareth; Ericsson, Hans; Ahnoff, Martin; Gislen, Kristina; Fager, Gunnar; Gustafsson, David
CORPORATE SOURCE: AstraZeneca R and D Molndal, Moelndal, S-431 83, Swed.
SOURCE: Drug Metabolism and Disposition (2003), 31(3), 294-305
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The absorption, metabolism, and excretion of the oral direct thrombin inhibitor, ximelagatran, and its active form, melagatran, were sep. investigated in rats, dogs, and healthy male human subjects after administration of oral and i.v. single doses. Ximelagatran was rapidly absorbed and metabolized following oral administration, with melagatran as the predominant compound in plasma. Two intermediates (ethyl-melagatran and OH-melagatran) that were subsequently metabolized to melagatran were also identified in plasma and were rapidly eliminated. Melagatran given i.v. had relatively low plasma clearance, small volume of distribution, and short elimination half-life. The oral absorption of melagatran was low and highly variable. It was primarily renally cleared, and the renal clearance agreed well with the glomerular filtration rate. Ximelagatran was extensively metabolized, and only trace amts. were renally excreted. Melagatran was the major compound in urine and feces after administration of ximelagatran. Appreciable quantities of ethyl-melagatran were also recovered in rat, dog, and human feces after oral administration, suggesting reduction of the hydroxyamidine group of ximelagatran in the gastrointestinal tract, as demonstrated when ximelagatran was incubated with feces homogenate. Polar metabolites in urine and feces (all species) accounted for a relatively small fraction of the dose. The bioavailability of melagatran following oral administration of ximelagatran was 5 to 10% in rats, 10 to 50% in dogs, and about 20% in humans, with low between-subject variation. The fraction of ximelagatran absorbed was at least 40 to 70% in all species. First-pass metabolism of ximelagatran with subsequent biliary excretion of the formed metabolites account for the lower bioavailability of melagatran.
IT 192939-72-3
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(absorption, distribution, metabolism, and excretion of ximelagatran, an oral direct thrombin inhibitor, in rats, dogs, and humans)

L6 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:99008 CAPLUS
DOCUMENT NUMBER: 139:62516
TITLE: Determination of ximelagatran, an oral direct thrombin inhibitor, its active metabolite melagatran, and the intermediate metabolites, in biological samples by liquid chromatography-mass spectrometry
AUTHOR(S): Larsson, Marita; Ahnoff, Martin; Abrahamsson, Anna; Logren, Ulrika; Fakt, Christina; Ohrman, Irene; Persson, Bengt-Arne
CORPORATE SOURCE: DMPK and Bioanalytical Chemistry, AstraZeneca R and D Molndal, Moelndal, S-431 83, Swed.
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2003), 783(2), 335-347
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Anal. methods for the determination of ximelagatran, an oral direct thrombin inhibitor, its active metabolite melagatran, and intermediate metabolites, melagatran hydroxyamidine and melagatran Et ester, in biol. samples by liquid chromatog. (LC) pos. electrospray ionization mass spectrometry (MS) using selected reaction monitoring are described. Isolation from human plasma was achieved by solid-phase extraction on octylsilica. Analytes and isotope-labeled internal stds. were separated by LC utilizing a C18 anal. column and a mobile phase comprising acetonitrile-4 mmol/L ammonium acetate (35:65, volume/volume) containing 0.1% formic acid, at a flow-rate of 0.75 mL/min. Absolute recovery was .apprx.80% for ximelagatran, .apprx.60% for melagatran Et ester, and >90% for melagatran and melagatran hydroxyamidine. Limit of quantification was 10 nmol/L, with a relative standard deviation <20% for each analyte and <5% above 100 nmol/L. Procedures for the determination of these analytes in human urine and breast milk, plus whole blood from rat and mouse are also described.
IT 192939-72-3, Melagatran hydroxyamidine
RL: ANT (Analyte); ANST (Analytical study)
(ximelagatran and its active metabolite melagatran and intermediate metabolites determination in biol. samples by liquid chromatog.-mass spectrometry)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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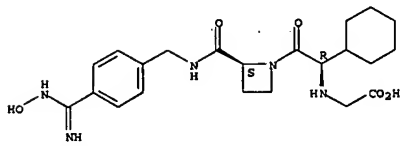
L6 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:506597 CAPLUS
DOCUMENT NUMBER: 127:136080
TITLE: Preparation of peptide derivatives as prodrugs of thrombin inhibitors
INVENTOR(S): Antonsson, Thomas; Gustafsson, David; Hoffmann, Kurt-Jurgen; Nystrom, Jan-Erik; Sorensen, Henrik; Sellen, Mikael
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9723499	A1	19970703	WO 1996-SE1680	19961217
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9610353	A	19970623	ZA 1996-10353	19961209
TW 541316	B	20030711	TW 1996-85115209	19961209
TW 238827	B	20050901	TW 2002-91115525	19961209
CA 2238737	A1	19970703	CA 1996-2238737	19961217
AU 9712178	A	19970717	AU 1997-12178	19961217
AU 706350	B2	19990617		
EP 869966	A1	19981014	EP 1996-943446	19961217
EP 869966	B1	20050316		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1209139	A	19990224	CN 1996-180024	19961217
CN 1127510	B	20031112		
HU 9900115	A2	19990528	HU 1999-115	19961217
BR 9612148	A	19990713	BR 1996-12148	19961217
JP 2000504313	T	20000411	JP 1997-523571	19961217
JP 3282821	B2	20020520		
EP 995755	A1	20000426	EP 1999-120315	19961217
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NZ 324902	A	20000623	NZ 1996-324902	19961217
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RU 2176644	C2	20011210	RU 1998-111148	19961217
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L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PT 869966	T	20050729	PT 1996-943446	19961217
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PRIORITY APPLN. INFO.:

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SE 1996-556	A	19960215
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JP 1997-523571	A3	19961217
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SE 1997-4542	A	19971205
WO 1998-SE2191	A	19981201
US 1999-353644	A1	19990715
US 2000-708449	B1	20001109
US 2002-74008	B1	20020214

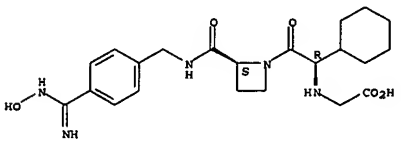
OTHER SOURCE(S): MARPAT 127:136080

AB Title compds. of formula R1O(O)C-CH2-(R)Cgl-Aze-Pab-R2 [wherein R1 = H, C1-10 alkyl, (un)substituted C1-3 alkylphenyl, A1C(O)N(R3)R4, A1C(O)OR3; (R)Cgl = (R)-cyclohexyl glycine; Aze = (S)-azetidine-2-carboxylic acid; Pab = 1-amidino-4-aminomethylbenzene; R2 (which replaces one of the hydrogen atoms in the amidino unit of Pab) = OH, OC(O)R5, C(O)OR6, C(O)OCH(R7)OC(O)R8; R3 and R4 are independently e.g., H, C1-6 alkyl, Ph, or together with the nitrogen atom represent pyrrolidinyl or piperidinyl; R5 = C1-17 alkyl, Ph, or 2-naphthyl (all of which are optionally substituted by C1-6 alkyl or halogen); R6 = (un)substituted 2-naphthyl, Ph, C1-3 alkylphenyl, C1-12 alkyl; R7 = H, C1-4 alkyl; R8 = e.g., 2-naphthyl, Ph, C1-6 alkoxy, (un)substituted C1-8 alkyl] or a pharmaceutically acceptable salt thereof, which are useful as prodrugs of inhibitors of trypsin-like proteases (no data), such as thrombin, and in particular in the treatment of conditions where inhibition of thrombin is required (e.g. thrombosis) or as anticoagulants, were prepared For example, EtO2C-CH2-(R)Cgl-Aze-Pab-COOCH2CH:CH2 was prepared via coupling of Me3CO2C-(R)Cgl-Aze-Pab-H with allyl chloroformate followed by Boc deprotection and coupling with Et bromoacetate. The title compds. were all found to exhibit oral and/or parenteral bioavailability in rats as the active inhibitor HO2C-CH2-(R)Cgl-Aze-Pab-H, either as the free acid and/or as one or more ester thereof.

IT 192939-72-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of peptide derivs. as prodrugs of thrombin inhibitors)

RN 192939-72-3 CAPLUS
CN Glycine, N-[(1R)-1-cyclohexyl-2-[(2S)-2-[[[[4-[(hydroxyamino)iminomethyl]phenyl]methyl]amino]carbonyl]-1-azetidinyl]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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FULL ESTIMATED COST                                     74.75     248.41

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